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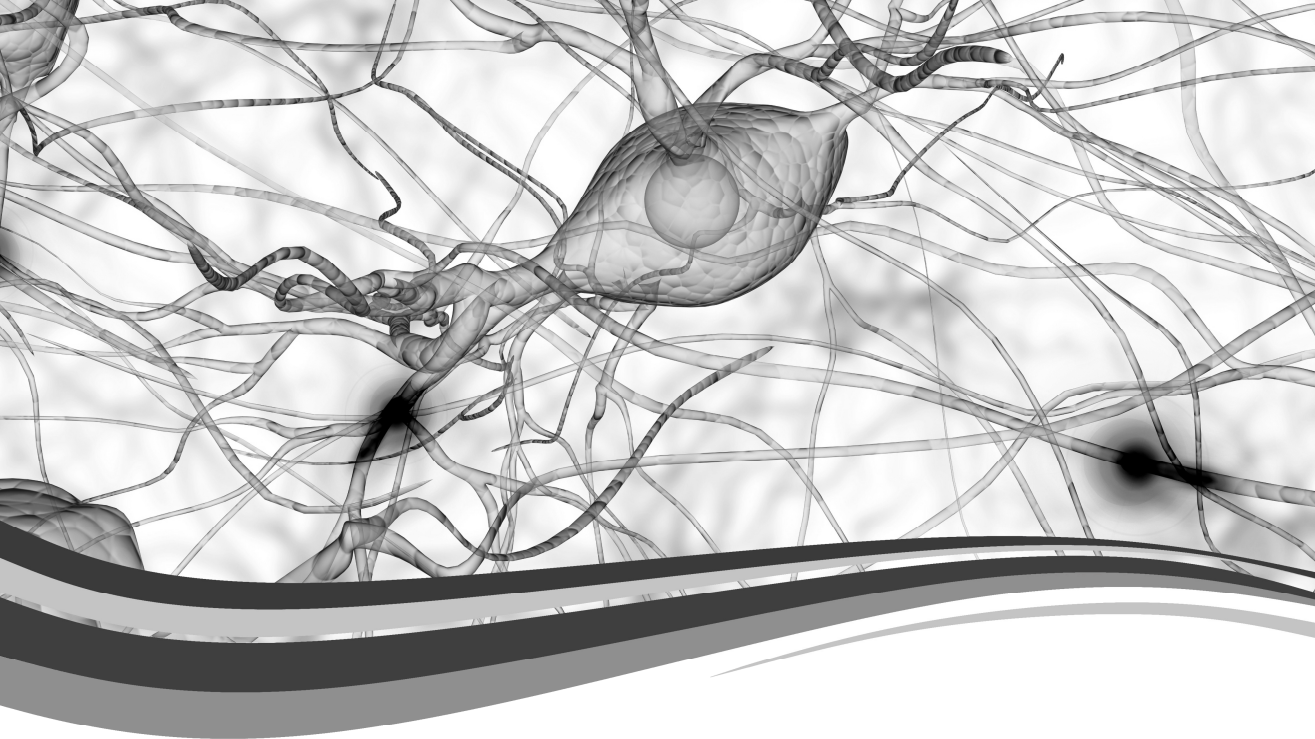
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Chapter 4 The presence of depression and anxiety do not distinguish between functional myoclonic jerks and cortical myoclonus

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4.1 Abstract

Introduction | Functional movement disorders are accompanied by a high occurrence of psychopathology and cause serious impairments in quality of life. However, little is known about this in patients with functional jerks and no comparison has been made between patients with functional jerks and organic myoclonus. This case control study compares the occurrence of depression, anxiety and quality of life (HR-QoL) in patients with functional jerks and cortical myoclonus.

Methods | Patients with functional jerks and cortical myoclonus, consecutively recruited, were compared on self-rated anxiety (Beck Anxiety Inventory), depression (Beck Depression Inventory), health-related quality of life (RAND-36), and myoclonus severity (UMRS and CGI-S rating scales).

Results | Sixteen patients with functional jerks and 23 with cortical myoclonus were evaluated. There was no significant difference in depression (44% vs. 43%) or anxiety (44% vs. 47%) scores between groups. The HR-QoL was similarly impaired except that functional jerks patients reported significantly more pain ($p < 0.05$). Only in the functional jerks group myoclonus severity correlated with depression and anxiety.

Conclusion | Depression and anxiety scores are high and do not discriminate between functional jerks and cortical myoclonus. Quality of life was equally impaired in both sub-groups, but pain was significantly worse in patients with functional jerks.

4.2 Introduction

Functional movement disorders (FMD) are disabling involuntary movements, which can be defined by incongruence with known neurological pathology and the influence maneuvers like distraction and suggestion. One of the manifestations of FMD is functional myoclonic jerks (FJ), which has a prevalence amongst FMD of approximately 15%.¹

FJ is characterized by an acute onset of jerks with a slow or variable burst duration, an inconsistent distribution, and reduction with distraction.² Clinical discrimination between FJ and organic myoclonus can be very difficult, even for world class experts.³ In these cases, electrophysiological testing aids in the diagnosis of FJ, especially with the finding of a pre-movement or Bereitschaftspotential with back-averaging. Accurate and early diagnosing of FJ is important as prompt treatment improves patient's outcome.⁴ There is no evidence on specific therapy for FJ, but patient education and specialized physiotherapy are considered increasingly important in the treatment of FMD.⁵

Symptoms of depression and anxiety are more common in FMD than in healthy controls, with 37,1%-61% lifetime depression and 20% - 21% generalised anxiety disorder in two key publications.⁶ Although psychopathology has been found to be high in FMD,⁷ this is not unique for FMD as organic movement disorders are also often accompanied by psychopathology.⁸⁻¹⁰ Studies comparing FMD with organic neurological disorders found either more affective disorders and anxiety in FMD, or equal prevalences.⁶ Furthermore, previous studies reported a similar level of impairment of the quality of life and daily functioning, for example when comparing FMD with Parkinson's Disease.⁷⁻¹¹ In multiple movement disorders there is an ongoing discussion whether psychiatric co-morbidity are primary and part of the phenotype or a secondary consequence of the motor disorder.⁸⁻¹²

Little is known about the psychiatric co-morbidity in patients with FJ, and, to date, there has been no systematic comparison with an appropriate control group. In our study we explored the depression and anxiety rate, and whether these psychiatric symptoms and the perceived health related quality of life could discriminate between FJ and cortical myoclonus (CM). Based on the literature, our hypothesis is that patients with FJ experience more symptoms of depression, anxiety, and have a greater impairment of their quality of life.

4.3 Methods

4.3.1 Recruitment

Adult patients with FJ and CM were consecutively recruited from both the outpatient clinic and the ward of the Neurology department of our tertiary referral centre between May 2014 and June 2016. Patients were excluded if they were aged less than 16, or were judged to have significant cognitive impairment interfering with ability to complete measures. In all patients a comprehensive history was taken, including age at onset, co-existing neurological symptoms, and non-neurological co-morbidity. All subjects previously participated in a study about the value of electrophysiological testing in determination of the myoclonus subtype (*article under review*).

The Ethical Board of the University Medical Center Groningen (UMCG) approved the study (Number M14.157933).

4.3.2 Motor assessment

All patients underwent a medical history, protocolled videotaped clinical examination and electrophysiological testing. The diagnosis CM or FJ was made by a movement disorder specialist (MT) based on clinical characteristics. Co-existing neurological symptoms including additional movement disorders were recorded.

Severity of myoclonus was scored by two independent experts using the modified versions of the Unified Myoclonus Rating Scale (UMRS)¹³ and the 7 point Global Clinical Impression - Severity (GCI-S) scale.¹⁴ The average score of the two experts was used.

4.3.3 Psychiatric and quality of life assessment

Participants were asked to fill out a questionnaire consisting of the Beck anxiety Inventory (BAI)¹⁵, and the Beck depression inventory (BDI).¹⁶ For the BDI, we used a cut-off score of 10 or higher to distinguish depressive from non-depressive patients, the range for mild depression was 10-19, moderate 19-29 and severe 30-63.¹⁶ For the BAI the same scores were used to divide symptoms into no, mild, moderate and severe anxiety.¹⁷ Three items on the BAI concerning trembling or shaking of several body parts were excluded from analysis, without adjustment of the marking of the BAI, as these questions are

inherent to the movement disorders studied. The RAND 36 questionnaire, a Dutch validated version of the SF36 was used for measuring quality of life.¹⁸

4.3.4 Statistical analysis

Chi-square tests were used for categorical variables and Mann-Whitney U tests for ordinal and continuous not-normally distributed data in SPSS 23. When differences between groups were found, odds ratios were calculated using binominal logistic regression analysis, to provide predictive value of the factor for being in one of the groups. Inter-rater reliability for video motor scoring was assessed using the intra-class correlation coefficient (ICC) (Two way mixed, consistency, average measures). Correlations between physical functioning (RAND-36 subscale), depression (BDI), anxiety (BAI) and symptom severity (CGI), were calculated using Spearman's correlation in both groups. No violations were noted of the completed statistical analyses. All statistical tests were two-sided. The p-values of <0.05 were considered as statistically significant.

4.4 Results

4.4.1 Participants characteristics

Forty-seven adult patients, including 27 with CM and 20 FJ were recruited. Three CM cases were excluded from the study due to cognitive problems and five cases (4FJ and 1CM) had not completed the questionnaires.

In total 39 patients; 16 FJ (69% female, median age at examination 32 years) and 23 CM patients (52% female, median age at examination 30 years) participated in the study.

The severity of myoclonus on the UMRS was significantly higher for FJ (FJ:16.5, CM: 5.7) without a significant difference in CGI-S (FJ:4, CM:3) with a good ICC between raters (ICC UMRS = 0.98 (95% CI: 0.95-0.99) / ICC CGI-S = 0.82 (95% CI: 0.67- 0.91)).

Co-existing neurological symptoms were detected in five of the 20 FJ and in nine of the 27 CM patients (Table 1).

In the CM group, in 15/23 cases an aetiological diagnosis was made; five had an acquired cause, 10 cases were thought to have a genetic origin of which a causative gene mutation was found in seven cases (see Supplementary Table 1). The demographic features are shown in Table 1.

Table 1 - Demographic features, psychiatric co-morbidity and quality of life in functional jerks versus cortical myoclonus patients

	CM (n=23)	FJ (n=16)
Female N (%)	12 (52%)	11 (69%)
Age at examination, median (IQR)	30 (32)	32 (38)
Age at onset of myoclonus, median (IQR)	17 (39)	25 (36)
Total UMRS, median (IQR)	5,7 (15)	16,5 (14)*
Total GCI-S, median (IQR)	3 (4)	4 (4)
Medical history		
epilepsy	5	0
cognitive problems	4	0
structural brain damage	3	1
Other neurological symptoms		
dystonia	5	0
ataxia	4	0
spasticity	0	1
other functional symptoms	0	4
Median RAND-36 scores (IQR)		
Physical functioning	60 (56)	75 (63)
Social functioning	63 (38)	63 (59)
Role limitation physical	50 (100)	12,5 (94)
Role limitation emotional	100 (100)	100 (50)
Mental health	76 (32)	78 (20)
Vitality	50 (30)	50 (30)
Pain	80 (33)	49 (52)*
General health perception	40 (15)	50 (35)
Expected health change	50 (25)	50 (50)
Median BDI (range) (cut-off scores)	9 (0 - 25)	7 (0 - 43)
No depression (0-9)	13	9
Mild depression (10-18)	7	4
Moderate depression (19-29)	3	1
Severe depression (30-63)	0	2
Median BAI (range)	7 (0 - 26)	7 (3 - 28)
No anxiety (0-9)	12	9
Mild anxiety (10-18)	7	4
Moderate anxiety (19-29)	4	3
Severe anxiety (30-63)	0	0

Supplementary Table 1 - Aetiological diagnosis

Etiological diagnosis		CM (n=23)	
Genetic disorder	Genetic mutation identified	Wilson disease (mutation <i>ATP7B</i> gene)	1
		Niemann pick type C (<i>NPC1</i> mutation)	2
		Lafora disease (mutation <i>NHLRC1</i> gene)	1
		Ramsay Hunt syndrome (<i>GOSR</i> mutation)	1
		Myoclonus dystonia (<i>RELN</i> mutation)	1
		Myoclonus Dystonie (chromosome 18p-)	1
	No genetic mutation identified	Juvenile myoclonus epilepsy	1
		Ramsay Hunt syndrome	1
		Myoclonus dystonia	1
	Acquired disorder	Medication-induced	1
Metabolic derangements		2	
Structural cerebral lesion		2	
Unknown		8	

4.4.2 Occurrence of depression, anxiety, and health related quality of life

As is shown in Table 1, in the FJ group, 7/16 (44%) met criteria for a mild to severe depression and in the CM group this was 10/23 (43%). The median depression score on the BDI was not significantly different between the FJ and CM groups (FJ: 7 (0-43), CM: 9 (0-25), $p=0.72$).

Seven of 16 (44%) FJ patients and 11/23 (48%) CM patients met criteria for mild to severe anxiety. The median BAI score was not significantly different for FJ (6 (0-28)) compared to CM patients (7 (0-26)).

On all subdomains of HR-QoL FJ and CM patients were equally impaired, except for the subdomain of pain. FJ patients reported significantly more pain (FJ vs CM median 49 (IQR 52) vs median 80 (IQR 33), $p<0.05$). Details about HR-QoL subdomains and severity of depression and anxiety can be found in Table 1.

As is shown in Table 2, myoclonus severity was correlated to both depression and anxiety in the FJ group, but not in the CM group. Pain was correlated to physical functioning in CM but not in FJ.

Table 2 - Correlations between myoclonus severity, psychiatric co-morbidity and HR-QoL

	Physical functioning (RAND36)		Myoclonus severity (mean CGI-S)	
	FJ	CM	FJ	CM
Myoclonus severity (mean CGI-S)	Rho -0,08 P=0.77	Rho -0,11 P=0.61	X	X
Depression (BDI)	Rho -0,27 P=0.33	Rho -0.12 P=0.60	Rho 0.49, p = 0.05	Rho 0.18, p = 0.42
Anxiety (BAI -corrected)	Rho -0,03 P=0,91	Rho -0.02 P=0.91	Rho 0.73, p <0.05	Rho 0.36, p = 0.09
Pain (RAND36)	Rho 0.40 P=0,12	Rho 0.47 p <0.05	Rho -0,25 P=0,34	Rho 0,31 P=0,14

BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, CGI-S: Global Clinical Impression - Severity, CM: cortical myoclonus, FJ: functional jerks. Statistically significant correlations using Spearman's Rho ($p < 0.05$) are highlighted in bold.

4.5 Discussion

In this prospective study, we showed functional jerks and cortical myoclonus patients had equally high depression and anxiety scores and a similar impaired health related quality of life. Patients with FJ reported significantly more pain compared to the CM group.

The occurrence of mild to severe depression and anxiety in both FJ and CM found in our cohort is high compared to the normal population. In FJ, this confirms earlier findings in several types of functional neurological disorders.⁷ Psychiatric co-morbidity in a heterogeneous group of CM has not been studied before, but our results are comparable with the rates of anxiety and depression reported in CM patients diagnosed with Familial Cortical Myoclonic Tremor and Epilepsy and Juvenile Myoclonus Epilepsy.^{19,20} These findings might implicate that cortical myoclonus syndromes in general are associated with psychiatric co-morbidity. In myoclonus dystonia (M-D) psychiatric comorbidity has consistently been described.¹⁰ However, as M-D has a subcortical anatomical origin rather than cortical, a direct comparison with CM cannot be made. All in all, the similar levels of depression and anxiety in FJ and CM underline current views that these symptoms are not diagnostically relevant for FJ. The findings do, however, emphasize the importance for treatment of looking for anxiety and depression in both patient groups.⁵

Health related quality of life was similarly impaired in FJ and CM patients, as was hypothesized based on the literature.^{7,11} Pain was the only HRQoL subdomain significantly higher in the FJ group (median 49 (IQR 52) vs median 80 (IQR 33), $p < 0.05$). Pain has been reported to be high in other subtypes of

FMD, mainly functional (fixed) dystonia.²¹ The relation between FJ and pain has not been studied before. Our finding implies that pain might be a promising diagnostic tool to discriminate FJ from other jerky movements, but this requires further studies in a larger prospective cohort.

Myoclonus severity was found to correlate with anxiety and depression scores in FJ but not CM. This might suggest that in the FJ group, there is a bidirectional relationship between anxiety/depression and myoclonus. Previous studies have shown that chronic pain negatively influences mood and quality of life.²² However, in our cohort pain did not explain the relationship between anxiety/depression and myoclonus, as pain was not correlated to myoclonus severity. The lack of a relationship between anxiety/depression and myoclonus in CM suggest that these symptoms could be part of the CM phenotype or could be caused by other factors not taken into account in this study. To be able to determine whether the psychiatric symptoms have a primary or secondary cause, larger, preferably longitudinal, studies are required.

This study has limitations. As applies to all rare disorders, we had to study a small sample from a tertiary clinic, which improves diagnostic accuracy but might impair generalizability. Furthermore, using the BAI might have caused an overestimation of anxiety in both groups, as it largely measures the experience of physical complaints, which are partly influenced by having myoclonus. In order to minimize this overestimation, we have excluded questions directly related to jerky movements, while retaining the cut-off value.

In conclusion, this study showed high depression and anxiety scores and a comparable impairment of the quality of life in patients with FJ and CM, with significantly more pain in the FJ group. It is important for clinicians to be aware of the high appearance of depression and anxiety in myoclonic disorders as these symptoms often require treatment. Unfortunately, the presence of depression and anxiety cannot be used as a diagnostic tool for FJ, however, pain might be a significant marker of differentiation between organic myoclonus and functional jerks.

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